REMARKS

Claims 1-6 and 8-12 are pending and under examination.

Claims 4, 5, 8, 9, 11 and 12 have been amended herein to remove multiple dependencies. These amendments fully address the claim objections at page 2 of the current Office Action and do not raise an issue of new matter and entry thereof is respectfully requested.

Regarding 35 U.S.C. § 103

Applicants respectfully traverse the rejection of claims 1-5 and 8-12 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Fitzsimons et al., *Gene Therapy*, 8:1675-1681 (2001) in view of Nakagawa et al., *European Journal of Pharmaceutical Sciences* 13:53-60 (2001).

Applicant respectfully points out the following deficiencies with regard to the aforementioned rejection: (1) The references, viewed alone or in combination, do not teach or suggest all of the elements of the rejected claims, and (2) the claimed invention represents more than the predictable use of the elements described in the cited prior art as evidenced by the unexpected results described in detail below.

The examiner bears the burden of establishing a *prima facie* case of obviousness. *In re Rijckaert*, 9 F.3 1531, 1532, (Fed. Cir. 1993). Only if this burden is met does the burden of coming forward with rebuttal argument or evidence shift to the applicant. *Id.* at 1532. When the references cited by the examiner fail to establish a *prima facie* case of obviousness, the rejection is improper and will be overturned. *In re Fine*, 837 f.2d 1071, 1074 (Fed. Cir. 1988).

To support a *prima facie* finding of obviousness, it is required that the prior art references must teach or suggest all the claim limitations. *In re Royka*, 490 F.2d 981, 985 (CCPA 1974).

When the PTO shows *prima facie* obviousness, the burden then shifts to the applicant[s] to rebut." In re Mayne, 104 F.3d 1339, 1342, 41 USPQ2d 1451, 1454 (Fed. Cir. 1997). "Such rebuttal or argument can consist of a comparison of test data showing that the claimed compositions possess unexpectedly improved properties or properties that the prior art does not have..." In re Dillon, 919 F.2d 688, 692-93, 16 USPQ2d 1897, 1901 (Fed. Cir. 1990)(en banc).

A claimed invention is unobvious when it represents "more than the predictable use of prior art elements according to their established functions." *See KSR Int'l Co. v. Teleflex Inc., 127 S.Ct. 1727, 550 U.S. ___ (2007).* As disclosed in the specification, the claimed invention is more than the predictable use of prior art elements according to their established functions.

The current Office Action mailed January 28, 2008, misconstrues the concept of what constitutes unexpected results. In particular, the Office argues that unexpected results are precluded because the Fitzsimons vector has some of the same elements as the claimed vector (page 8, final sentence). This statement conveys a lack of understanding of the doctrine of unexpected results, which necessarily always applies in situations where each cited prior art reference contains at least some of the same elements as the claimed invention. Without prior art claiming elements of the invention, there would be no need to point out the unexpected results. The Office extends this argument by stating that the unexpected results are "inherent" in the combination of the two cited references. Applicants respectfully disagree. Unexpected results is not the same as predictable positive results, which may be what the Examiner means by use of the term "inherent." Even if, *arguendo*, a skilled person would expect positive results from the combination of Fitzsimons and Nakagawa, Applicants respectfully submit that the exhibits submitted with the submission filed November 5, 2007, show, not predictable, but unexpected, synergistic results that would not be expected by the skilled person.

Applicants respectfully request that the Office review the arguments and exhibits with the proper standard for applying the doctrine of unexpected results and consider the evidence that the skilled person familiar with the cited references would not have expected the significantly higher efficiency of gene expression and the higher suppression rates compared to the expression systems described in the cited references. As detailed in the exhibits and accompanying arguments in Applicants' last submission filed November 5, 2007, the high efficiency of gene expression observed with the vectors of the present invention represents an unexpected result that amounts to much more than the predictable use of the prior art elements according to their established functions. The question is whether the result is synergistic and adds up to more than the sum of its parts, more what would be expected by the skilled person.

In their previous response, Applicants pointed to the following evidence of unexpected results:

- Expression of the construct described by Fitzsimons et al. was less than two-fold higher as compared to expression in a plasmid (see Figure 4). Suppression (repression) is shown between 100-fold to 200-fold with a maximum at 204-fold (Block et al., *Journal of Gene Medicine* 5:190-200 (2003), Exhibit 1 to Applicants submission filed November 5, 2007, Figures 5 and 7). Fitzsimons only discloses constructs expressing luciferase, whereas constructs containing IL12 or other transgenes are not disclosed at all.

- Gene expression for the claimed adenoviral vector construct is much higher than for the Fitzsimons et al. rAAV vector. For example, for a construct containing IL12 as transgene, up to 1,000 µg/24 h/106 cells could be expressed in a linear, m.o.i. dependent fashion for various cell lines using the same transgene (IL12) in 48 hours at a m.o.i. of 10 (expression of up to 200 µg). (Block et al., *Journal of Gene Medicine* 5:190-200 (2003)).

- High efficiency of gene expression was confirmed in various cell lines and for various transgenes with a comparable order of magnitude. The claimed construct provides 16,000-fold suppression for expression of the luciferase gene and 6,000-fold for IL12 expression. The order of magnitude of suppression was also completely surprising and unexpected by the skilled artisan. Exhibit 2 to Applicants submission filed November 5, 2007, is Figure 1, which shows expression of hIL12 following infection of human colon carcinoma cells with 10 m.o.i. and incubation over 24 hours using various concentrations of doxycyclin using the claimed adenoviral vectors. Determination of IL12 in supernatant and cell lysate is shown. The data obtained for the claimed vectors according to claim 1 support the unexpected high native expression and suppressibility achieved with the claimed vectors and represent their application in clinical studies.

- Due to the unexpected high suppressibility of IL12 expression, complete protection in C57B16 mice could be achieved by adding doxycyclin (Dox) to the drinking water following systemic application of a 100 % lethal vector dosage. Further, attached as Exhibit 3 to Applicants submission filed November 5, 2007, is Figure 2, which shows that intra-tumoral application led to highly significant tumor regression in all treated animals showing a long-term survival of 25%. Attached as Exhibit 4 to Applicants submission filed November 5, 2007, is Figure 3, which shows tumors after day 18. Well observable are large tumors under control (mock) or when using control vector Ad.DL312, whereas no tumors or only very small tumors were observed following application of vector Ad3r-IL12 of the invention.

- For the Examiner's convenience, the significant differences of the vector according to the invention as compared to the expression system according to Fitzsimons were shown in Table1 of Applicants' submission filed Noember 5, 2007.[1]

[1] The Office Action argues that Applicants made the incorrect comparison by comparing the Fitzsimmons vector to the claimed vector. Applicants respectfully disagree and point out that this is the only possible comparison. The

In sum, the skilled person would not have expected the high gene expression and suppressibility associated with the vector constructs of the current invention. Furthemore, nothing about the combination of these two references would give rise to a prediction or expectation of the *synergistic* results described above.

In view of the arguments above and the previously submitted exhibits and accompanying remarks submitted November 5, 2007, removal of the rejection of claims 1-5 and 8-12 under 35 U.S.C. §103(a) over Fitzsimons et al., supra, in view of Nakagawa et al., *European Journal of Pharmaceutical Sciences* 13:53-60 (2001) is respectfully requested.

Applicants respectfully traverse the rejection of claims 1 and 5-7 under 35 U.S.C. §103(a) over Fitzsimons et al., *supra*, in view of Lode et al., *European Journal of Pharmaceutical Sciences* 13:53-60 (2001).

The unexpected results achieved with the presently claimed vectors are described in the previously submitted exhibits and accompanying remarks submitted November 5, 2007, and reiterated above with additional arguments. Applicants maintain that the secondary reference by Lode et al. does not add anything of significance except that the authors teach single-chain IL12 fusion protein. The publication is completely silent as to the cassette bearing the transgene and the combination of Fitzsimons et al. and Lode et al. provides no expectation of the results described above.

In view of the arguments above and the previously submitted exhibits and accompanying remarks submitted November 5, 2007, removal of the rejection of claims 1 and 4-7 under removal of the rejection of claim 6 under 35 U.S.C. §103(a) over Fitzsimons et al., *supra*, in view of Lode et al., *European Journal of Pharmaceutical Sciences* 13:53-60 (2001) is respectfully requested.

---

point of the comparison is to show that insertion of the Fitzsimons cassette into the Nagakawa adenovirus vector would hardly be expected to result in efficiencies that are increased by over 10,000% as shown for the claimed vector.

CONCLUSION

In light of the remarks herein, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect. The Examiner is invited to call the undersigned attorney if there are any questions.

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 502624 and please credit any excess fees to such deposit account.

Respectfully submitted,

McDERMOTT WILL & EMERY LLP

/Astrid R. Spain/

Astrid R. Spain
Registration No. 47,956

4370 La Jolla Village Drive, Suite 700
San Diego, CA 92122
Phone: 858.535.9001 ARS:cjh
Facsimile: 858.597.1585
Date: July 28, 2008

Please recognize our Customer No. 41552 as our correspondence address.